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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,913	08/06/2001	Zuomei Li	106101.145	8110

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EXAMINER	
LACOURCIERE, KAREN A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,913	LI ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-37 and 44-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-37 and 44-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-09-2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group III and SEQ ID NO:2 in the paper filed 11-14-2003 is acknowledged.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specifically, alterations have been made in the address of inventors Li and Bonfils, which have not been initialed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-37 and 45-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34-37 and 45-48 are dependent upon cancelled claims 1 or 3, which have been canceled. Claims 34-37 and 45-48 are directed to methods which use an agent specified in claims 1 or 3, however, there is no way to determine what agent is used in the claimed methods. Therefore, it is not possible to determine what methods are being claimed. Claims 34-37 and 45-48 are so unclear and cannot be searched, therefore, claims 34-37 and 45-48 have not been further treated on the merits.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 44 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 44 is directed to methods of inhibiting cell proliferation by administering a broad genus of agents selected from antisense to a histone deacetylase, small molecule inhibitors of histone deacetylase, antisense to a DNA methytransferase and small molecule inhibitors of DNA methytransferases.

The specification discloses the 17 antisense sequences targeted to forms of human histone deacetylases, including HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8, and three small molecule inhibitors of histone deacetylases. These histone deacetylase inhibitors meet the written description provisions of 35 USC 112, first paragraph. The specification does not describe any antisense or small molecule inhibitors of DNA methyltransferases. However, claim 44 is directed to encompass a broad range of types of inhibitors, of highly variant structure, and nucleic acid based inhibitors to generally any species or variant form of histone deacetylases or DNA methyltransferases, which have not been described in the specification and whose structure could not be envisioned by the skilled artisan based on the disclosure if the specification. Although some DNA methyltransferase inhibitors were described in the art, at the time of the invention the art recognized that the structure of such inhibitors was not sufficiently known. For example, Fournel et al. state (in 1999) "direct evidence that elevated DNA MeTase levels alter gene expression and influence oncogenesis has been difficult to obtain, in part due to the lack of specific DNA MeTase inhibitors." (see abstract). It appears that the prior art did not describe a sufficient number of species of DNA methyltransferase inhibitors, to describe the broad genus, and the disclosure of the specification does not provide any additional description beyond that of the prior art, as they do not provide the structure of any DNA methyltransferase inhibitors. Additionally, although some histone deacetylase inhibitors were known, but the proteins encompassed in the genus of histone deacetylases is very broad. For example, Bestor et al. discuss that there are many different pathways for

deacetylation, and that many transcription regulators actually posses that activity. Therefore, the genus of histone deacetylases is very broad and antisense and small molecule inhibitors of such is also incredibly broad. Given the broad class of compounds encompassed in the claimed methods and the variety of both the targets for inhibition and the variety of structures of inhibitors used in the claimed methods, the disclosure of the specification is a very small number of species of the broad genus and provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of antisense targeted to the human forms of HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8 and the disclosed small molecule inhibitors of histone deacetylase disclosed and the DNA methyltransferase inhibitors disclosed in the prior art (as represented by Fournel et al.), the skilled artisan cannot envision the detailed chemical structure of the encompassed inhibitors used in the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and

Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

The full breadth of the claim does not meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claim 44 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of cell proliferation in vitro and inhibition of cell proliferation using a combination of a histone deacetylase small molecule inhibitor and a DNA methyltranferase small molecule inhibitor, does not reasonably provide enablement for inhibition of cell proliferation using an antisense inhibitor of a histone deacetylase or DNA methyltransferase in vivo in a whole organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claim 44 is drawn broadly to inhibition of cell proliferation of a cell in any setting, including in vivo in a whole organism. The specification contemplates use of such methods for the purpose of therapy, including for the treatment of cancer. These methods encompass the use of combinations which include the use of antisense targeted to a histone deacetylase or a DNA methyltransferase or a combination of antisense targeted to both types of enzymes.

The specification provides examples wherein antisense targeted to histone deacetylase inhibited tumor cell growth in cells *in vitro* (cell culture) in human cell lines. The specification does not provide any examples on the use of antisense targeted to any DNA methyltransferase, nor does it provide any examples of the use of antisense targeted to histone deacetylase or DNA methyltransferase in combination with any small molecule inhibitors. The specification does not demonstrate any correlation with the inhibition of histone deactylase or DNA methyltransferase in cell culture using antisense and a treatment for any cell proliferation disease. The specification does not present any examples wherein antisense targeted to histone deactylase or DNA methyltransferase was delivered to cells *in vivo* (whole organism), nor wherein antisense targeted to histone deactylase or DNA methyltransferase inhibited the proliferation of in cells *in vivo* (whole organism), either together or in combination with any small molecule inhibitor. The specification does not present any guidance on how to target any cells in vivo to inhibit proliferation, particularly wherein the proliferation results in a treatment effect.

At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for

unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed. The specification provides examples wherein antisense is delivered to cells *in vitro* and the expression of histone deacetylase is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition for antisense due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences and the potential for non-antisense side

effects. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. This unpredictability is amplified for the claimed methods wherein a combination of antisense to histone deacetylase is used in combination with antisense targeted to DNA methyltransferase, as it would require the specific and effective delivery of two different antisense molecules.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to histone deactylase and/or DNA methyltransferase to generally any target cell or tissue *in vivo* (whole organism) at an effective concentration.

In order to practice the invention claimed, over the full scope claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of how to effectively target and delivery an effective concentration of antisense, or an effective combination of antisense to specific cells to a target cell *in vivo* (whole organism) to inhibit cell proliferation, particularly to achieve a treatment effect. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense molecule *in vivo*. Given the art recognized unpredictability of the therapeutic application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods of treatment claimed, the state of the art of antisense, the level of unpredictability of *in vivo* (whole organism) methods of using antisense, the lack of specific guidance for the *in vivo* (whole organism) application of antisense methods and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods of claim 44 over the full scope claimed without undue trial and error experimentation.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or

discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 44 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6, and 11-34 of copending Application No. 09/420,692. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 44 of the instant application is drawn to inhibiting proliferation of a cell by administering a combination of a least two agents, including a combination of a methyltransferase antisense and a small molecule inhibitor of methyltransferase. The methods of instant claim 44 encompasses the methods of claims 1-3, 6 and 11-34 of 09/420,692, which are drawn to methods of inhibiting the expression of human DNA methyltransferase gene in a cell, including a cell in a human, by administering a methyltransferase

antisense and a protein effector, including small molecule inhibitors of the methyltransferase.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 44 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 42-48 of copending Application No. 10/051,819. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claim 44 is drawn to methods of inhibiting proliferation in a cell comprising administering at least two agents, including an antisense inhibitor of a histone deacetylase and a small molecule inhibitor of a histone deacetylase, which encompasses the methods of inhibiting cell proliferation in a cell in an animal by administering an inhibitor of HDAC-4 and an antisense targeted to HDAC-1, as claimed in 10/051,189.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 44 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37-39 of copending Application No. 10/052,390. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claim 44 is drawn to methods that include inhibiting cell proliferation by administering at least two agnets

including an antisense inhibitor of histone deacetylase and a small molecule inhibitor of histone deacetylase. The methods of claim 44 overlap in scope with the methods of claims 37-39 of co-pending application 10/052,390, which include methods of inhibiting cell proliferation in a cell in an animal using a small molecule inhibitor of histone deacetylase and an antisense molecule targeted to HDAC-1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 44 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 and 11-50 of copending Application No. 10/145,493. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claim 44 is drawn to methods of inhibiting cell proliferation by administering at least two agents selected from inhibitors of histone deacetylase and DNA methyltransferase, including antisense and small molecules, these methods overlap in scope with the methods of claims 1-8 and 11-50, which include inhibiting cell proliferation by administering a combination of agents including inhibitors of histone deacetylase and DNA methyltransferase, including antisense and small molecules.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 44 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 21 and 22 of copending Application No. 09/563,728. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 44 of the instant application is drawn to methods of inhibiting cell proliferation by administering an antisense targeted to histone deacetylase and a small molecule inhibitor of DNA methyltransferase, which encompasses inhibiting neoplastic cell growth in a mammal by administering an antisense to histone deacetylase and a histone deacetylase protein inhibitor, as claims in 09/563,728.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical

Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 44 rejected under 35 U.S.C. 102(b) as being anticipated by Jones et al. (Nature Genetics, Vol. 19, June 1998, pages 187-191).

Jones et al. disclose contacting a cell with TSA, a small molecule inhibitor of histone deacetylase, and a DNA methylase repression protein (MeCP2 repression domain, Gal4-MRD), which falls within the broad scope of the term "DNA methyltransferase small molecule inhibitor" (see for example page 189). Jones et al. do not explicitly state that proliferation of the cells is inhibited, but the method of Jones et al. comprises all of the steps of the claimed method and, absent evidence to the contrary, would be expected to inherently inhibit proliferation.

Claim 44 is rejected under 35 U.S.C. 102(b) as being anticipated by Nan et al.

Nan et al. disclose contacting mouse L929 fibroblast cells with the histone deacetylase inhibitor TSA and the transcriptional repression domain (TRP) of MeCP2 which falls within the broad scope of the term "DNA methyltransferase small molecule inhibitor" (see for example page 388). Nan et al. do not explicitly state that proliferation of the cells is inhibited, but the method of Nan et al. comprises all of the steps of the claimed method and, absent evidence to the contrary, would be expected to inherently inhibit proliferation.

Claim 44 is provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 09/420,692 which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application.

Claim 44 of the instant application is drawn to inhibiting proliferation of a cell by administering a combination of a least two agents, including a combination of a methyltransferase antisense and a small molecule inhibitor of methyltransferase. Co-pending Application SN 09/420,692, discloses and claims methods of inhibiting the expression of human DNA methyltransferase gene in a cell, including a cell in a human, by administering a methyltransferase antisense and a protein effector, including small molecule inhibitors of the methyltransferase.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

Claim 44 is provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 09/563,728 which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application. Claim 44 of the instant application is drawn to methods of inhibiting cell proliferation by administering an antisense targeted to histone deacetylase and a small molecule inhibitor of DNA methyltransferase. 09/563,728 discloses and claims methods of inhibiting neoplastic cell growth in a mammal by administering an antisense to histone deacetylase and a histone deacetylase protein inhibitor.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (571) 272-0759. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Lacourciere
February 5, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER